MINISTRY OF HEALTH
SCOTTISH HOME AND HEALTH DEPARTMENT

CENTRAL HEALTH SERVICES COUNCIL
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SAFETY OF DRUGS

Final Report of the Joint Sub-Committee of the Standing Medical Advisory Committees.

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JOINT SUB-COMMITTEE ON SAFETY OF DRUGS

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STANDING MEDICAL ADVISORY COMMITTEES (ENGLAND AND WALES AND SCOTLAND)

JOINT SUB-COMMITTEE ON SAFETY OF DRUGS

FINAL REPORT

Terms of reference

1. We were set up by the Standing Medical Advisory Committees for both England and Wales and Scotland in August 1962 with the following terms of reference:—

> "to advise the Minister of Health and the Secretary of State for Scotland on what measures are needed:—
>
> (i) to secure adequate pharmacological and safety testing and clinical trials of new drugs before their release for general use;
>
> (ii) to secure early detection of adverse effects arising after their release for general use; and
>
> (iii) to keep doctors informed of the experience of such drugs in clinical practice".

Interim advice

2. In view of the widespread public concern following the thalidomide episode we thought it desirable, before proceeding to examine in detail the wide range covered by our terms of reference, to tender early interim advice with regard to the present arrangements for testing new drugs for toxicity before they are used in clinical trials. This advice, which was submitted to the Health Ministers on 2nd November, 1962, comprised the following three main recommendations:—

(1) The responsibility for the experimental laboratory testing of new drugs before they are used in clinical trials should remain with the individual pharmaceutical manufacturer.

(2) It is neither desirable nor practicable that at this stage of their evaluation the responsibility for testing drugs should be transferred to a central authority.

(3) There should be an expert body to review the evidence and offer advice on the toxicity of new drugs, whether manufactured in Great Britain or abroad, before they are used in clinical trials. The Sub-Committee proposed, in the light of further consideration and consultations, to formulate detailed advice on the composition and terms of reference of this advisory body.

3. On 6th November the Minister of Health announced that the Government had accepted the first two recommendations and would await our promised advice on the third.

4. In presenting our interim advice we stressed that the safety of a drug was relative not absolute. Its safety depended on the drug's toxicity as revealed in laboratory tests and in its clinical use, and on its efficacy. The frequency of adverse reactions was one of the factors to be considered in assessing the therapeutic worth of a drug. Some drugs which carried a recognised hazard in therapeutic doses might yet be justifiably used in the treatment of disease. For example a high incidence of adverse reactions could

be tolerated if a drug cured or stayed the progress of a grave disease such as cancer or leukaemia but no significant toxicity should be tolerated in a new hypnotic for which there were many less toxic equivalents.

Further consultations

5. Since tendering our interim advice we have received memoranda from and met representatives of the Association of British Pharmaceutical Industry, the British Medical Association, the Pharmaceutical Society of Great Britain and the College of General Practitioners.

Scope of Report

6. We have interpreted our remit as requiring us to advise on measures which, firstly, will ensure that the practice of all manufacturers in the toxicity testing and clinical trial of new drugs conforms with the highest standards in this respect; secondly, will re-assure the public that all possible steps are being taken to prevent the marketing of new drugs which have not been the subject of adequate safety testing and clinical trial; and, thirdly, will reveal at the earliest possible time adverse reactions in humans which have not been unmasked in toxicity tests and clinical trials.

Need for further legislation

7. There are several other aspects of drug safety which are of considerable importance, e.g., the control of quality of drugs, control of sale over the counter, labelling of containers, use of approved names, regulation of therapeutic claims, etc. These matters, new arrangements for which would require legislation, are outside our terms of reference. Our concern is with arrangements for ascertaining the effects of drugs and we make recommendations accordingly. These arrangements themselves would obviously be more effective with legislative sanction than without and we are satisfied that legislation on the whole subject is urgently required. No interim measures should be regarded as a justification for delaying this essential task. We recognise, however, that legislation would probably involve a comprehensive review of the whole field and that this is a major undertaking. Yet there is a specially urgent need to take whatever steps are immediately possible to improve the safety testing of drugs. The scheme we suggest can be introduced, if desired, without waiting for legislation. In the absence of legislation, it will only be effective to the extent that the industry and the medical profession are prepared to co-operate in implementing it but we hope it is reasonable to assume that this co-operation will be forthcoming.

Composition and functions of the Committee on Safety of Drugs

8. We have already expressed the view that the pharmaceutical industry as a whole discharges its responsibilities for the experimental laboratory testing of new drugs effectively within the limits of existing knowledge of methods of testing. Public and professional opinion will, nevertheless, demand some type of formal machinery, independent of that of the manufacturer, for the assessment of the safety of a drug in relation to the purpose for which it is to be used. We do not think this warrants any elaborate or large-scale system of control.

9. There are three clearly defined stages in the testing of a new drug, viz.

(i) Toxicity tests on animals, and possibly on human volunteers, before a drug, which is thought to be promising pharmacologically, is used in clinical trials.

(ii) Clinical trials designed to test efficacy; to establish the best formulation and dosage; to confirm that there are no short-term, unacceptable side effects (careful attention should be paid to risks for special groups such as pregnant women); and to determine whether a drug is habit-forming.

(iii) General release, during which other adverse reactions might begin to appear, possibly not before several years had elapsed.

10. We think that a Committee on the Safety of Drugs should be established with sub-committees to advise it on each of the three aspects, namely :—

(i) toxicity;
(ii) clinical trials and therapeutic efficacy; and
(iii) adverse reactions.

The function of the parent body would be generally to guide and co-ordinate the activities of the sub-committees who should have power to consult outside experts where they see fit. There would be some overlap of membership between the parent body and the sub-committees. We recognise that our proposal to add yet a further committee to the multiplicity of bodies with functions in the field of drugs will impose additional demands on available expertise which is already heavily engaged. This we fear is inevitable. The Committee would require the support of one or more salaried experts (especially in the field of toxicity testing) and a qualified secretariat.

Alternative suggestions made to us

11. We have considered the proposal by the Association of British Pharmaceutical Industry for an advisory centre on drug safety under a Trust independent of Government and of industry. Under these arrangements Trustees would appoint an Executive Committee to supervise the administration of the advisory centre. The Executive Committee would be empowered to seek advice from a consultative panel of outside experts and would appoint a permanent staff under a scientifically qualified Director. The Director would receive protocols and advise individual firms on the adequacy of their toxicity tests for particular drugs; and, in consultation with the person undertaking the clinical trials, would advise firms on the adequacy of the data submitted to him for the purpose of establishing the safety of a drug before general release.

12. The A.B.P.I. thought that a body of this kind, appointed as a Trust, and reinforced by advice on standards and methodology of toxicity testing from their own expert Committee and that established by the Medical Research Council, would command authority and ensure independence. They objected to linking the advisory centre with the Health Ministers on the grounds that it might become entangled in political issues.

13. The A.B.P.I.'s proposal seems to us to have a number of important defects. In our view, public opinion is unlikely to be content with anything short of Ministerial responsibility for verifying that adequate precautions, in the light of current medical and scientific knowledge, have been taken to

secure the safety of drugs, the more so because of the number and nature of new drugs. The proposal that the industry should give financial support to the centre, even if subject to a Trust Deed, would detract from the value of the centre which, in our view, must be clearly seen to be independent of industry. Furthermore, it is by no means certain that the Association's proposal would command the co-operation of all non-member firms, importers and foreign manufacturers. The high standards of leading firms are not necessarily reproduced throughout the industry.

14. The British Medical Association supported the industry in urging that the Health Ministers should not appoint the Committee on Safety of Drugs, on the grounds that their National Health Service responsibilities would arouse the suspicion that their actions would be coloured by political motives and considerations of economy. These organisations thought that if such a body were to be linked with Government it should be appointed by the Privy Council.

Constitution and functions of the Committee

15. We cannot accept that it would be proper for the Privy Council to appoint the proposed Committee. In view of the Minister of Health's responsibility under the Ministry of Health Act 1919 for the health of the nation and the responsibility of the Secretary of State for Scotland under the corresponding Scottish Acts, we have no doubt that the Health Ministers should appoint the Committtee. We think their wider responsibility is clearly distinguishable from their responsibility to provide a National Health Service. It would be for them to appoint a new Committee, after consultation with the relevant interests, which should include the Royal Colleges, the General Medical Council, the Medical Research Council, the British Medical Association and the Pharmaceutical Society of Great Britain. In our view, public opinion would require that it should be entirely independent of industry. While the Committee or any of its sub-committees might feel a need from time to time to seek advice on certain matters from experts in industry, we do not think that direct representation of industry on these bodies would necessarily be in its own interests.

Toxicity Tests

16. We have already tendered advice on the toxicity testing of new drugs. The principal function of the Committee in this respect would be to satisfy itself, through the medium of a main sub-committee on toxicity, on the basis of protocols and other evidence submitted by or on behalf of the manufacturers, that before a drug was submitted for clinical trials it had been subject to adequate toxicity testing, and to advise the manufacturers accordingly. The latter would no doubt have recourse to advice and guidance which may be made available from time to time by the expert committees set up by the Medical Research Council and the Association of British Pharmaceutical Industry or from other sources.

17. It would be open to the Committee to decide whether, exceptionally, and subject to conditions, individual drugs or groups of drugs might safely be submitted to clinical trials before the completion of toxicity testing.

Clinical trials

18. We have been informed that the industry have experienced little, if any, difficulty in making arrangements with suitable consultants for the clinical

trials of new drugs showing promise of marked therapeutic advance but they claim to have difficulties with drugs of probable marginal advantage over existing remedies. The industry already know, or can ascertain from known sources, the names of persons who are competent and willing to undertake trials for them and we think that the responsibility of deciding whom they should approach for assistance in this respect should be left with individual manufacturers. We see no advantage in establishing a formal register of persons able and willing to undertake clinical trials.

19. In order to limit the hazards, the initial clinical trials should be confined to one or two centres. Where two or more centres are involved the names of the investigators should be known by any participant so that helpful communication can, if necessary, be established. The wide distribution of drugs for clinical trial is not to be encouraged.

20. The responsibility for arranging clinical trials should lie with the manufacturer. In some special cases the Medical Research Council might be prepared to arrange these trials; in others, university or hospital departments or individual consultants may accept responsibility for the trial.

21. There should be an independent objective assessment of clinical trials by the second sub-committee who would have regard to evidence submitted by the manufacturer and the consultant concerned. If any toxic reactions occur during the clinical trial they should be notified immediately to the main Committee.

22. In our Interim Report we expressed the view that the safety of a drug is relative and not absolute. It depends on a number of considerations including the efficacy of the drug and the nature of the conditions for which it is to be used. Accordingly, the function of the parent Committee at this stage should be to determine, on the advice of the second sub-committee, whether, in the case of a drug which had been the subject of clinical trials, the evidence before it was sufficient to establish the adequacy of the trials and the safety of the drug in relation to the conditions for which it was intended to be used.

23. The Committee might then decide that the drug could be safely released for general use. If, however, it were satisfied that the drug has clinical value and is relatively safe it might decide that longer trial under controlled conditions, e.g. in hospitals or on special prescriptions, should be continued before the drug's release for general use.

24. We do not believe that the procedures we have outlined for the assessment of toxicity testing and clinical trials need impose any substantial or unnecessary delay in the development of a drug for general use. The Committee and sub-committees would be expected to meet frequently in order to discharge their duties expeditiously. If some delay is inevitable it is a small price to pay for as great an assurance of safety as possible.

Sanctions under a Voluntary Scheme

25. While a voluntary scheme could have no formal legal sanctions, we think that the following measures might help, nevertheless, to ensure that new drugs were subject to adequate toxicity testing and clinical trials :—

(i) It should be accepted practice that no doctor should agree to undertake a clinical trial of a drug without an assurance that full data on its

toxicity tests had been seen and approved by the Committee on Safety of Drugs.

(ii) If a manufacturer decided to release a drug, which had passed the stage of clinical trial, for general use contrary to the Committee's advice, the facts should be brought immediately to the attention of all prescribers.

(iii) Similarly, if it came to the notice of the Committee that a manufacturer had marketed a drug without giving the Committee an opportunity to assess the adequacy of any toxicity tests or clinical trials which might have been carried out, all prescribers should be informed of the facts.

We do not think that the Committee itself should be expected to bring these facts directly to the attention of the medical profession since this might lay the Committee open to action through the Courts. In our view, the Committee should advise the Health Ministers whenever such instances occurred so that the Ministers might take whatever action they thought fit to bring the facts to the notice of the profession.

Central Registry of Adverse Reactions

26. Arrangements for the prompt identification and early reporting of adverse reactions of new drugs form an essential part of any system for ensuring the safety of drugs. The international recognition of this need is reflected in the intention of the World Health Organisation at its Assembly in June 1963 to consider specific proposals for establishing an international registry of drug toxicity. We think that the collation and assessment of reports of adverse reactions should be undertaken by a third sub-committee of the Committee on Safety of Drugs. While the existence of such a body could not of itself have averted the tragedies associated with the use of thalidomide, the collection and early dissemination of information about side effects might have shortened the period between recognition of its toxic hazards and withdrawal of the drug. Even the elaborate machinery operating in those countries such as the U.S.A. does not give a complete guarantee of safety. Late toxic effects from drugs have led to the withdrawal of approval given earlier in many instances. In the U.S.A. thalidomide tablets were sent to 1,270 doctors for investigation and given to 20,771 patients. It was the long delay imposed on marketing the drug in the U.S.A. which allowed the harmful effects of thalidomide to be reported from elsewhere. This emphasises the need for an international, as well as a national, registry.

27. It should be left to the Committee on Safety of Drugs and the appropriate sub-committee to determine the machinery for the submission and reporting of data about suspected side effects. There are various ways in which such information could be brought to their attention, viz.

(i) The family doctor has clearly an important part to play in collecting such information. All practitioners who are prepared to do so might report to the appropriate sub-committee of the proposed new Committee, on simple record cards, or through regional reporting centres based on teaching hospitals and large non-teaching hospitals with whom local groups of general practitioners could make easy contact. The College of General Practitioners have already established a small

registry and have indicated their willingness to co-operate in the work of a permanent central organisation.

(ii) Hospital specialists, in particular haematologists and dermatologists, either individually or through their associations, might be invited to watch for and report any side effects.

28. We feel sure that the pharmaceutical industry would wish to play a full part in the provision of a service of this kind. Individual manufacturers would be prepared no doubt to provide the sub-committee with full information about adverse effects of their products. In return they would expect access to information about their products which might be passed to the sub-committee from other sources.

29. Such evidence as is available does not suggest that in the early stages the Committee is likely to be overwhelmed with reports of adverse reactions. The need to ensure that reactions following the administration of a drug are not necessarily caused by it will not be overlooked by those responsible for the registry. They will need effective and accurate machinery for the analysis of records and work closely with the branches of the Health Departments responsible for the analysis of prescription statistics.

30. Evaluation of reports of adverse reactions should be quantitative as well as qualitative. Statistical data available through National Health Service sources about the extent to which individual drugs are prescribed would provide an opportunity for making a quantitative assessment of the hazards involved.

31. We believe that it should be the responsibility of the Health Ministers to arrange for the dissemination of information about adverse reactions, and that some formal machinery should be established to ensure that this is done at regular intervals.

Drugs to be submitted to the new Committee

32. We recommend that all new drugs and preparations be submitted to the Committee on Safety of Drugs. Of these, which may number 300 or more a year, only 30–40 will be "new" in the sense of drugs of new chemical structure or novel therapeutic action. Only for these latter is it likely that the full machinery of the Committee will need to be brought into play, but it is, in our view, essential that the degree of testing necessary for all preparations should be determined by the Committee.

(Signed on behalf of the Sub-Committee)

COHEN OF BIRKENHEAD.

E. L. MAYSTON, *Secretary.*

March, 1963.

NOTE OF DISSENT BY MR. J. GROSSET AND SIR HUGH LINSTEAD

1. We regret that we are not able to agree with the advice offered by our colleagues except upon the formation of a Central Registry of Adverse Reactions.

2. *Central Registry of Adverse Reactions*

We agree that it will be valuable to set up a centre to collect and collate information about untoward effects from drugs and to disseminate reports and information.

3. *Voluntary or Statutory Control of Toxicity Testing and Clinical Trials?*

Our main disagreement with our colleagues lies in the answer to this question. They favour a voluntary system until time can be found for legislation. We believe that any voluntary system must have so many loopholes that it can offer no real additional safeguards to the public. In consequence we consider that there is no satisfactory alternative to early legislation.

4. *The Deficiencies of a Voluntary Scheme*

The following are the most important defects in a voluntary scheme:—

(*a*) Such a scheme depends upon the co-operation of the whole of the pharmaceutical industry. It is not certain that this will be secured. In particular, it will not be enough for the leading firms to give it their support if smaller firms with inadequate research and testing facilities fail to do so.

(*b*) The sanctions that can be applied in any voluntary scheme are few and weak. Members of the Association of the British Pharmaceutical Industry can be subjected to domestic disciplinary control, but this is not effective for non-members and exclusion from the Association is no barrier against continuing in business. Notification to the medical profession by the Minister of Health that a particular drug has not been approved will have some effect, but the manufacturer can counteract it by propaganda if he feels that the withholding of approval is unjustified. Firms can justify non-co-operation on the ground that their products have been adequately tested abroad and are registered there. If by this sort of justification they can secure six months lead over their more scrupulous rivals they will be strongly tempted to do so, and such conduct will soon erode the scheme. It is also said that if an unapproved drug were to cause toxic effects the manufacturer would be hard put to it to defend himself if he were sued for damages. Yet a manufacturer may well feel safe in relying upon tests undertaken abroad and upon the fact that a drug has been approved as safe by the appropriate authority of another country. Sanctions such as these therefore will tend to put the less scrupulous manufacturer (who may be prepared to take risks) at an advantage over his more scrupulous or co-operative competitor.

(*c*) A voluntary scheme may therefore offer more than it can perform and may give the appearance of safety without the reality.

5. We know of no other countries comparable in their scientific and industrial development with our own that have not found it necessary to control drugs by statute.

6. *Omissions from a Voluntary Scheme*

In addition to the positive defects of a voluntary scheme it suffers from the omission of many features essential to the proper control of drugs. For example :—

(*a*) It is almost certainly desirable that all new drugs should be restricted to medical prescription at least until their safety has been proved beyond question.

(*b*) There are some drugs (not necessarily poisons in the legal sense of the term) that the public should at no time be able to obtain except on production of a medical prescription.

(*c*) It is important that, whoever markets it, a drug shall always be called by the same name, preferably an internationally or nationally approved name, even when a trade marked name is also used.

(*d*) There are labelling requirements which ought to be imposed for the proper protection of the public, for example, a date after which a drug should not be used or a warning about possible dangers.

(*e*) Under a voluntary scheme a drug may be approved for one therapeutic purpose and later recommended by the makers for another. No voluntary scheme can control the therapeutic advice given to the medical profession about a new drug.

(*f*) There is no machinery for the continued oversight of drugs after they have been approved. For quite valid reasons their formulation may be changed or they may be combined with new ingredients.

(*g*) Except in the case of "therapeutic substances" and "dangerous drugs" there is no control over manufacture.

(*h*) There are defects in the present statutory provisions for ensuring that drugs are adequately packed by manufacturers so as to guard against deterioration.

7. *The Present Chaos of Authorities*

There is at present a series of bodies with varying authority, voluntary and statutory, over medicines. For example, narcotics are controlled by the Home Secretary with power to legislate by regulation. Poisons are also controlled by the Home Secretary with power to legislate, but in this case he acts on the advice of the Poisons Board. "Therapeutic substances" (essentially biological products) are controlled by the Health Ministers, again with power to legislate and again with the advice of an advisory committee, but a different one. The Pharmaceutical Society, the British Pharmacopoeia Commission, the Board of Trade, the Committee on the Classification of Proprietary Preparations (The Cohen Committee) and local authorities have also varying degrees of authority in this field. Enforcement is shared between inspectors of the Pharmaceutical Society, the Home Office and police, the Health Ministries and local food and drugs authorities. To justify the creation even temporarily of another body, independent of most of these, requires very convincing proof that the public

will thereby receive protection which would otherwise not be afforded to them. We believe that this case has not been made out for a body lacking statutory powers.

8. *One Central Authority*

What is needed is the creation by statute of a body of experts with the responsibility for advising the Health Ministers upon the control needed in the public interest over the whole field of medicines. This body would assume many of the diverse responsibilities indicated above. One of its functions would clearly be the supervision of toxicity testing and clinical trials and for this purpose it could set up a group of committees such as our colleagues propose. These committees would then be statutory bodies and not voluntary, they would be keyed in to the larger structure and there would be teeth in their decisions. Only then would all new drugs, with no exceptions, be subjected to review.

9. The present legislation regulating the manufacture and distribution of medicines has recently been reviewed by a departmental working party of the Ministry of Health. If a further enquiry is needed before legislation can be prepared, it should be put on foot now and arrangements for toxicity testing and clinical trials would clearly be included in such a review. It may be said that this involves delay and that a voluntary scheme, with all its defects, is preferable because it can be started quickly. If a voluntary scheme could furnish substantially better safeguards than exist at present there would be force in this argument. We do not believe, however, that within the field of toxicity testing and clinical trials a voluntary scheme is likely to add appreciably to the safeguards provided, and to be provided, by the industry aided by the advice of the Medical Research Council's Committee and the Central Registry of Adverse Effects. We see no danger in a temporary delay while a statutory scheme is evolved and the necessary legislation passed. Once this has been done, but not before, it will be possible to assure the public of full protection against toxicity and other dangers from drugs. We think it is more important to do the job thoroughly than to take refuge in what, at its best, can only be an expedient.

10. These are the reasons why, with regret, we differ from our colleagues and why we advise the Ministers

(1) not to initiate a voluntary scheme for the supervision of toxicity testing and clinical trials ; but

(2) to set on foot, with or without further enquiry, the preparation of a comprehensive statute dealing with drugs and medicines which will bring the whole field, including the supervision of toxicity testing and clinical trials, under the responsibility of the Health Ministers advised by a central body of experts.

JOHN GROSSET.

HUGH LINSTEAD.

March, 1963.

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